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(54) Title: ABUSE RESISTANT TABLETS

(57) Abstract

This invention relates to an abuse resistant tablet containing two or more layers comprising one or more drugs and one or more gelling agents wherein the drug(s) and gelling agent(s) are contained in separate layers of the tablet. The multilayer tablet is particularly suitable for the administration of drugs prone to abuse by unauthorised parenteral administration such as analgesics, hypnotics and anxiolytics.

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ABUSE RESISTANT TABLETS

This invention relates to abuse resistant tablets, to a process for their preparation, and to their use in therapy. More particularly, the present invention relates to abuse resistant tablets comprising a plurality of layers.

It is known that many drugs intended for legitimate oral use have the potential for abuse, whereby the drug may be extracted from a solid oral dosage form to provide a solution which may be used for unauthorised, unsupervised, illegal and/or dangerous parenteral administration. One way of substantially reducing or even eliminating this potential for drug abuse is to suppress or inhibit the extractibility of the drug from the composition comprising the drug. In US Patent No. 4,070,494 this is reported to have been achieved by incorporating in the composition an aqueous gelable material present in sufficient quantity to form a gel when combined with that volume of water otherwise necessary to dissolve all of the medicinal agent. US Patent No. 4,070,494 describes enteral compositions, including single and bilayer tablets, wherein the drug with potential for abuse is mixed with the gelling agent and in the case of a tablet is then pressed according to a conventional procedure. However, such tablets comprising a gelling layer are liable to seriously retard the release of the drug substance.

We have now found that release of the drug substance from a tablet comprising a gelling agent is improved if the drug substance and the gelling agent are present in separate layers of the tablet.

The present invention thus pertains to a tablet containing two or more layers comprising one or more

drugs and one or more gelling agents, characterised in that the drug(s) and gelling agent(s) are contained in separate layers of the tablet.

For the avoidance of doubt, it should be appreciated that the tablet may comprise separate layers one stacked on top of the other in a sandwich arrangement, or may comprise a core layer of gelling agent surrounded by one or more layers comprising one or more drugs. The sandwich arrangement is generally preferred.

Optionally the tablet has a coating which may or may not be a modified or sustained release coating.

Suitable drugs which may be incorporated into the abuse resistant tablets of the present invention include those which are particularly liable to abuse, for example, analgesics, hypnotics and anxiolytics.

Specific examples of analgesic drugs which may be incorporated into tablets of this invention include commercially available analgesic drugs, such as codeine, pethidine, methadone and morphine.

Specific examples of hypnotic agents which may be incorporated into tablets of this invention include benzodiazepines such as temazepam, nitrazepam, flurazepam and loprazolam and non-benzodiazepines such as chlormethiazole, zopiclone and zolpidem, and barbiturates such as butobarbitone, phenobarbitone and amylobarbitone.

Specific examples of anxiolytic agents which may be incorporated into tablets of this invention include diazepam, medazepam, oxazepam and lorazepam.

The term "gelling agent" as used herein refers to a material which forms a gel by the action of an aqueous medium, such as water or an aqueous solution of an organic acid (e.g. aqueous citric or acetic acid), a base (e.g. sodium bicarbonate or sodium tetraborate solution) or alcohol (e.g. an aqueous lower alkanol such as aqueous ethanol or isopropanol).

Suitable gelling agents include, but are not limited to, modified celluloses such as hydroxypropylmethylcellulose, hydroxypropyl-ethylcellulose, methylcellulose, sodium carboxymethylcellulose, and hydroxyethylcellulose, sodium alginate, alginic acid, tragacanth, polyacrylic acid and xanthan, guar, locust bean and karaya gums. Mixtures of two or more gelling agents may also be used.

Hereinafter, the layer or layers of the tablet containing the drug is referred to as the "active layer" and the layer or layers containing the gelling agent is referred to as the "gelling layer".

The viscosity of the gelling agent in the gelling layer will generally be within the range of about 1000cp to about 100,000cp. As used herein, the term "cp" refers to centipoise which is a standard unit of viscosity. One centipoise (cp) is equivalent to one millipascal second (mPa.s).

Preferably, the gelling agent will have a viscosity within the range of about 4,000cp to about 100,000cp. More preferably, the gelling agent will have a viscosity within the range of about 10,000cp to about 100,000cp.

It will be appreciated that the amount of gelling agent required in the tablet depends upon features such as the nature of the active constituent, the nature of the other excipients in the tablet, the weight of the tablet and the viscosity grade of the gelling agent. The amount of gelling agent present is preferably such that substantially no filterable material remains when the tablet is triturated with the minimal amount of aqueous medium needed to extract the drug. In general, the proportion of gelling agent by weight in the gelling layer is from about 10 to about 70%, preferably about 20 to about 60%, and most preferably about 30 to about 50%. The total amount of gelling layer in the tablet depends upon the relative proportion of active and gelling layers but may typically be in the range of about 20 to about 80% and preferably about 50 to about 80% by weight.

The amount of drug in the active layer depends upon the therapeutic dose required, as in conventional tablets. In general, the quantity of drug which is incorporated into each tablet is often from about 0.5mg to about 200mg by weight, preferably from about 1mg to about 100mg, and most preferably from about 1mg to about 50mg. In the case of zopiclone the quantity of drug which is incorporated into each tablet is preferably about 1mg to about 10mg.

The remainder of the active and gelling layers may consist of standard tablet excipients known to those in the art, including but not limited to diluents such as lactose, starches, cellulose and calcium hydrogen phosphate, disintegrants such as starches, modified starches, celluloses and modified celluloses, binders, glidants and lubricants.

The tablet may also contain materials known in the art intended for the modification of release characteristics of the drug.

Preferably the active layer and the gelling layer are substantially identical in colour and appearance, so that the join is not readily visible to the potential abuser.

A coating, which may or may not be a modified or sustained release coating, may advantageously be applied to a tablet according to the present invention. A coated tablet is potentially advantageous when the tablet layers are stacked in a sandwich construction in that the join between the active layer and the gelling layer is further disguised.

In tablets according to the invention with more than two layers, one surface of the active layer should be exposed to prevent retardation of release of drug substance. Since one surface of the active layer is always exposed and not in contact with the gelling layer in tablets according to the present invention, release of drug can proceed relatively uninhibited and at a rate substantially similar to that of conventional tablets which do not possess a gelling layer.

In contrast, a combination of the active drug substance and gelling agent in the same layer has the disadvantage that the gelling action is likely to retard the release of the drug in a manner similar to some known sustained release products which include water-swellable high molecular weight polymers to retard drug release. Reduction of the gelling agent concentration to a level which would not inhibit

release of the drug substance severely limits the abuse resistance potential of the tablet.

Drugs which may be particularly suitable for incorporation into the active layer of a tablet according to the present invention include zopiclone, temazepam, diazepam, zolpidem, codeine, methadone, pethidine, phenytoin and phenobarbitone. A preferred drug for use according to the present invention is zopiclone.

Gelling agents which may be particularly suitable for incorporation into the gelling layer of a tablet according to the present invention include modified celluloses and other high molecular weight polymers. Preferred gelling agents include modified celluloses such as hydroxypropylmethylcellulose, carboxymethylcellulose and methylcellulose and xanthan gum, especially hydroxypropylmethylcellulose.

A preferred tablet of the present invention is a bilayer tablet in which one layer comprises a drug and the other layer comprises a gelling agent. However, the invention also covers further multilayered tablets such as trilayered tablets.

It is to be understood that the present invention covers all appropriate combinations of particular and preferred moieties comprised within a tablet of the present invention as described herein.

According to a further feature of the invention there is provided a process for the preparation of a tablet of the present invention, which comprises forming the separate active and gelling layers, then combining the layers in a suitable tabletting machine, optionally

followed by the application of a coating using a conventional coating procedure.

Tablets of the sandwich arrangement may conveniently be prepared by a multistage compression process using a suitable tablet press, where the first layer is compressed from a suitable powder and one or more additional layers are compressed on top of the first or subsequent layers to form a bilayer or multilayer tablet.

Tablets comprising a core of gelling layer surrounded by an active layer may conveniently be prepared by first forming the core from a suitable powder by compressing the powder using a suitable tablet press. Thereafter, the core may be enclosed within the active layer or surrounded by a cap of active layer using conventional means, such as using a tablet press designed for compression coating.

Presses for the preparation of multilayer tablets according to the present invention are either commercially available or may be provided by modification of standard tabletting equipment.

Suitable coatings for tablets of the present invention include film coatings to provide immediate release of the drug. Suitable film forming materials include hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, polyvinylpyrrolidone, polyethylene glycols and acrylic polymers. Suitable film forming materials to provide modified or sustained release include ethylcellulose, fats and waxes, shellac, acrylic esters and phthalate or mellitate derivatives of cellulose ethers and polyvinyl ethers. The flexibility and performance of the film coat may be improved by the addition of

plasticisers such as polyhydric alcohols, acetate and phthalate esters, glycerides and oils.

According to a further aspect of the present invention there is provided a method of treating a patient requiring an analgesic, hypnotic or anxiolytic drug, which method comprises administering to said patient said drug comprised within a tablet according to the invention.

The following Examples illustrate the invention, but are not intended to limit the invention in any way.

Example 1

Part A

Zopiclone	6.00%w/w
Lactose	18.52%w/w
Calcium hydrogen phosphate	35.12%w/w
Maize starch	35.12%w/w
Sodium starch glycollate	5.00%w/w
Magnesium stearate	0.24%w/w

The components, with the exception of the magnesium stearate and the maize starch, were mixed together and then granulated using a paste containing the maize starch. The granules were dried, screened to obtain a suitable particle size distribution and mixed with the magnesium stearate.

Part B

Hydroxypropylmethylcellulose (100,000cp)	30.0%w/w
Calcium hydrogen phosphate	59.2%w/w
Croscarmellose sodium	10.0%w/w
Colloidal silica	0.3%w/w
Magnesium stearate	0.5%w/w

The components, except the magnesium stearate, were mixed together in a blender. When these had been sufficiently blended the magnesium stearate was mixed with the powder.

Bilayer tablets each containing 7.5mg of zopiclone, weighing 375mg and containing 125mg of Part A and 250mg of Part B, and 9mm in diameter, were produced on a tablet press by a two stage pressing procedure whereby tablets of Part B were formed in the press and then Part A was added and the press operated again.

Example 2

Part A

Zopiclone	6.0%w/w
Lactose	30.8%w/w
Calcium hydrogen phosphate	61.4%w/w
Sodium starch glycollate	1.0%w/w
Colliodal silicon dioxide	0.3%w/w
Magnesium stearate	0.5%w/w

The components, except the magnesium stearate, are mixed together in a blender. When these have been sufficiently blended the magnesium stearate is mixed with the powder.

Part B

Hydroxypropylmethylcellulose	(100,000cp)	40.0%w/w
Calcium hydrogen phosphate		49.2%w/w
Croscarmellose sodium		10.0%w/w
Colloidal silicon dioxide		0.3%w/w
Magnesium stearate		0.5%w/w

The components, with the exception of the magnesium stearate, are blended together. When these have been sufficiently blended the magnesium stearate is mixed with the powder. The powder is compressed by means of

a tablet press and the tablets are subsequently sieved through a 1.5mm screen to provide a coarse powder.

Bilayer tablets each containing 7.5mg of zopiclone, weighing 375mg and containing 125mg of Part A and 250mg of Part B, and 9mm in diameter, are produced on a tablet press by a two stage pressing procedure whereby tablets of Part B are formed in the press and then Part A is added and the press is operated again.

Example 3

Part A

Zopiclone	6.0%w/w
Microcrystalline cellulose	25.0%w/w
Lactose	67.2%w/w
Sodium starch glycollate	1.0%w/w
Colloidal silicon dioxide	0.3%w/w
Magnesium stearate	0.5%w/w

The components, except the magnesium stearate, were mixed together in a blender. When these had been sufficiently blended the magnesium stearate was mixed with the powder.

Part B

Sodium carboxymethylcellulose (2,000cp)	35.0%w/w
Lactose	54.2%w/w
Sodium starch glycollate	10.0%w/w
Colloidal silicon dioxide	0.3%w/w
Magnesium stearate	0.5%w/w

The components, except the magnesium stearate, were mixed together in a blender. When these had been sufficiently blended, the magnesium stearate was mixed with the powder.

Bilayer tablets each containing 7.5mg of zopiclone, weighing 375mg and containing 125mg of Part A and 250mg of Part B, and 9mm in diameter, were produced on a tablet press by a two stage pressing procedure whereby tablets of Part B were formed in the press and then Part A was added and the press operated again.

Example 4

Part A

Zopiclone	6.00%w/w
Calcium hydrogen phosphate	92.2%w/w
Croscarmellose sodium	1.00%w/w
Colloidal silicon dioxide	0.3%w/w
Magnesium stearate	0.5%w/w

The components, except the magnesium stearate, were mixed together in a blender. When these had been sufficiently blended the magnesium stearate was mixed with the powder.

Part B

Methylcellulose (4,000cp)	24.6%w/w
Lactose	24.9%w/w
Calcium hydrogen phosphate	40.0%w/w
Croscarmellose sodium	10.0%w/w
Magnesium stearate	0.5%w/w

The components, except the magnesium stearate, were mixed together in a blender. When these had been sufficiently blended, the magnesium stearate was mixed with the powder.

Bilayer tablets each containing 7.5mg of zopiclone, weighing 375mg and containing 125mg of Part A and 250mg of Part B, and 9mm in diameter, were produced on a tablet press by a two stage pressing procedure

whereby tablets of Part B were formed in the press and then Part A was added and the press operated again.

Example 5

Part A

Zopiclone	6.0%w/w
Lactose	30.3%w/w
Calcium hydrogen phosphate	60.7%w/w
Sodium starch glycollate	2.5%w/w
Magnesium stearate	0.5%w/w

The components, except the magnesium stearate, were mixed together in a blender. When these had been sufficiently blended the magnesium stearate was mixed with the powder.

Part B

Xanthan Gum	30.0%w/w
Calcium hydrogen phosphate	59.2%w/w
Croscarmellose sodium	10.0%w/w
Colloidal silicon dioxide	0.3%w/w
Magnesium stearate	0.5%w/w

The components, except the magnesium stearate, were mixed together in a blender. When these had been sufficiently blended, the magnesium stearate was mixed with the powder.

Bilayer tablets each containing 7.5mg of zopiclone, weighing 375mg and containing 125mg of Part A and 250mg of Part B, and 9mm in diameter, were produced on a tablet press by a two stage pressing procedure whereby tablets of Part B were formed in the press and then Part A was added and the press operated again.

Example 6

Part A

Zopiclone	6.0%w/w
Calcium hydrogen phosphate	58.5%w/w
Microcrystalline cellulose	30.0%w/w
Crospovidone	5.0%w/w
Magnesium stearate	0.5%w/w

The components, with the exception of the magnesium stearate, are mixed together in a blender. When these have been sufficiently blended, the magnesium stearate is mixed with the powder.

Part B

Hydroxypropylmethylcellullose (100,000cp)	40.0%w/w
Calcium hydrogen phosphate	19.2%w/w
Lactose	29.0%w/w
Microcrystalline cellulose	5.0%w/w
Povidone K30	6.0%w/w
Colloidal silicon dioxide	0.3%w/w
Magnesium stearate	0.5%w/w

The components, with the exception of the colloidal silicon dioxide and the magnesium stearate, are blended together in a suitable mixer. The powder is then mixed with demineralised water until a granule is formed. The granule is dried and screened to obtain a satisfactory particle size. The screened granule is then blended with the colloidal silicon dioxide and the magnesium stearate.

Bilayer tablets, each containing 7.5mg of zopiclone, weighing 325mg and containing 125mg of Part A and 200mg of Part B and 9mm in diameter, are produced on a tablet press by a two stage compression procedure.

Tablets are film coated by applying a coating solution containing hydroxypropylmethylcellulose, polyethylene glycol and colorants using a suitable coating apparatus.

Example 7

Part A

Zopiclone	4.5%w/w
Lactose	19.4%w/w
Calcium Hydrogen Phosphate	36.4%w/w
Maize starch	36.4%w/w
Sodium starch glycollate	3.0%w/w
Magnesium stearate	0.3%w/w

The zopiclone, lactose, calcium hydrogen phosphate and some of the maize starch were mixed together in a blender and then mixed with a paste prepared from the remaining starch and demineralised water until a granule was formed. The granule was dried and passed through a screen to obtain a satisfactory particle size. The screened granule was then blended with the sodium starch glycollate and the magnesium stearate.

Part B

Hydroxypropylmethylcellullose (100,000cp)	40.0%w/w
Calcium hydrogen phosphate	19.2%w/w
Lactose	29.0%w/w
Microcrystalline cellulose	5.0%w/w
Povidone K30	6.0%w/w
Colloidal silicon dioxide	0.3%w/w
Magnesium stearate	0.5%w/w

The components, with the exception of the colloidal silicon dioxide and the magnesium stearate, were blended together in a suitable mixer. The powder was then mixed with demineralised water until a granule was formed. The granule was dried and screened to

obtain a satisfactory particle size. The screened granule was then blended with the colloidal silicon dioxide and the magnesium stearate.

(a) Bilayer tablets, each containing 7.5mg of zopiclone, weighing 365mg and containing 165mg of Part A and 200mg of Part B and 10mm in diameter, were produced on a tablet press by a two stage compression procedure; and

(b) Bilayer tablets, each containing 3.75mg of zopiclone, weighing 283mg and containing 83mg of Part A and 200mg of Part B and 9mm in diameter, were produced on a tablet press by a two stage compression procedure.

Tablets from (a) and (b) above were film coated by applying a coating solution containing hydroxypropylmethylcellulose, polyethylene glycol and suitable colorants using a suitable coating apparatus.

Example 8

Part A

Temazepam	10.0%w/w
Anhydrous Lactose	58.0%w/w
Microcrystalline cellulose	25.0%w/w
Croscarmellose sodium	6.0%w/w
Magnesium stearate	1.0%w/w

The components, with the exception of the magnesium stearate, are mixed together in a blender. When these have been sufficiently blended, the magnesium stearate is mixed with the powder.

Part B

Hydroxypropylmethylcellullose (100,000cp)	40.0%w/w
Lactose	34.2%w/w
Microcrystalline cellulose	25.0%w/w
Colloidal silicon dioxide	0.3%w/w
Magnesium stearate	0.5%w/w

The components, with the exception of the colloidal silicon dioxide and the magnesium stearate, are blended together in a suitable mixer. The powder is then blended with the colloidal silicon dioxide and the magnesium stearate.

Bilayer tablets containing 20mg of temazepam, weighing 400mg and containing 200mg of Part A and 200mg of Part B, and 9mm in diameter are produced on a tablet press by a two stage compression procedure.

Example 9

Part A

Diazepam	4.0%w/w
Lactose	30.5%w/w
Calcium hydrogen phosphate	35.0%w/w
Maize starch	25.0%w/w
Croscarmellose sodium	5.0%w/w
Magnesium stearate	0.5%w/w

The diazepam, lactose, calcium hydrogen phosphate and some of the maize starch and croscarmellose sodium are placed in a blender and then mixed with a paste prepared from the remaining starch and demineralised water until a granule is formed. The granule is dried and passed through a screen to obtain a satisfactory particle size. The screened granule is then blended with the remaining croscarmellose sodium and the magnesium stearate.

Part B

Hydroxypropylmethylcellullose (100,000cp)	40.0%w/w
Calcium hydrogen phosphate	19.2%w/w
Lactose	29.0%w/w
Microcrystalline cellulose	5.0%w/w
Povidone K30	6.0%w/w
Colloidal silicon dioxide	0.3%w/w
Magnesium stearate	0.5%w/w

The components, with the exception of the colloidal silicon dioxide and the magnesium stearate, are blended together in a suitable mixer. The powder is then mixed with demineralised water until a granule is formed. The granule is dried and screened to obtain a satisfactory particle size. The screened granule is then blended with the colloidal silicon dioxide and the magnesium stearate.

Bilayer tablets containing 5mg of diazepam, weighing 325mg and containing 125mg of Part A and 200mg of Part B, and 9mm in diameter are produced on a tablet press by a two stage compression procedure.

Example 10

Part A

Zolpidem hemitartrate	5.0%w/w
Lactose	64.5%w/w
Microcrystalline cellulose	25.0%w/w
Croscarmellose sodium	5.0%w/w
Magnesium stearate	0.5%w/w

The zolpidem hemitartrate, lactose and microcrystalline cellulose and croscarmellose sodium are mixed together in a blender. When these have been sufficiently blended, the magnesium stearate is mixed with the powder.

Part B

Hydroxypropylmethylcellullose (100,000cp)	40.0%w/w
Calcium hydrogen phosphate	19.2%w/w
Lactose	29.0%w/w
Microcrystalline cellulose	5.0%w/w
Povidone K30	6.0%w/w
Colloidal silicon dioxide	0.3%w/w
Magnesium stearate	0.5%w/w

The components, with the exception of the colloidal silicon dioxide and the magnesium stearate, are blended together in a suitable mixer. The powder is then mixed with demineralised water until a granule is formed. The granule is dried and screened to obtain a satisfactory particle size. The screened granule is then blended with the colloidal silicon dioxide and the magnesium stearate.

Bilayer tablets containing 5mg of zolpidem hemitartrate, weighing 325mg and containing 125mg of Part A and 200mg of Part B, and 9mm in diameter are produced on a tablet press by a two stage compression procedure.

Tablets are film coated by applying a coating solution containing hydroxypropylmethylcellulose, polyethylene glycol and suitable colorants using a suitable coating apparatus.

Example 11

Part A

Codeine Phosphate	10.0%w/w
Lactose	51.5%w/w
Maize starch	30.0%w/w
Povidone K30	5.0%w/w
Sodium starch glycollate	3.0%w/w
Magnesium stearate	0.5%w/w

The codeine phosphate, lactose, povidone and some of the maize starch are mixed together in a blender and then mixed with a paste prepared from the remaining starch and demineralised water until a granule is formed. The granule is dried and passed through a screen to obtain a satisfactory particle size. The screened granule is then blended with the sodium starch glycollate and the magnesium stearate.

Part B

Hydroxypropylmethylcellullose (100,000cp)	40.0%w/w
Calcium hydrogen phosphate	19.2%w/w
Lactose	29.0%w/w
Microcrystalline cellulose	5.0%w/w
Povidone K30	6.0%w/w
Colloidal silicon dioxide	0.3%w/w
Magnesium stearate	0.5%w/w

The components, with the exception of the colloidal silicon dioxide and the magnesium stearate, are blended together in a suitable mixer. The powder is then mixed with demineralised water until a granule is formed. The granule is dried and screened to obtain a satisfactory particle size. The screened granule is then blended with the colloidal silicon dioxide and the magnesium stearate.

Bilayer tablets containing 15mg of codeine phosphate, weighing 350mg and containing 150mg of Part A and 200mg of Part B, and 10mm in diameter are produced on a tablet press by a two stage compression procedure.

Example 12

Part A

Methadone hydrochloride	5.0%w/w
Lactose	39.0%w/w
Maize starch	27.5%w/w
Powdered cellulose	25.0%w/w
Sodium starch glycollate	3.0%w/w
Magnesium stearate	0.5%w/w

The components, with the exception of the sodium starch glycollate and the magnesium stearate and some of the maize starch, are blended together in a suitable mixer. The powder is then mixed with a paste prepared from the remaining starch and demineralised water until a granule is formed. The granule is dried and screened to obtain a satisfactory particle size. The screened granule is then blended with the sodium starch glycollate and the magnesium stearate.

Part B

Hydroxypropylmethylcellullose (100,000cp)	40.0%w/w
Calcium hydrogen phosphate	19.2%w/w
Lactose	29.0%w/w
Microcrystalline cellulose	5.0%w/w
Povidone K30	6.0%w/w
Colloidal silicon dioxide	0.3%w/w
Magnesium stearate	0.5%w/w

The components, with the exception of the colloidal silicon dioxide and the magnesium stearate, are blended together in a suitable mixer. The powder is then mixed with demineralised water until a granule is

formed. The granule is dried and screened to obtain a satisfactory particle size. The screened granule is then blended with the colloidal silicon dioxide and the magnesium stearate.

Bilayer tablets containing 5mg of methadone hydrochloride weighing 300mg and containing 100mg of Part A and 200mg of Part B, and 9mm in diameter are produced on a tablet press by a two stage compression procedure.

Example 13

Part A

Pethidine hydrochloride	25.0%w/w
Lactose	39.0%w/w
Maize starch	27.5%w/w
Povidone K30	5.0%w/w
Sodium starch glycollate	3.0%w/w
Magnesium stearate	0.5%w/w

The pethidine hydrochloride, lactose, povidone and some of the maize starch are mixed together in a blender and then mixed with a paste prepared from the remaining starch and demineralised water until a granule is formed. The granule is dried and passed through a screen to obtain a satisfactory particle size. The screened granule is then blended with the sodium starch glycollate and the magnesium stearate.

Part B

Hydroxypropylmethylcellullose (100,000cp)	40.0%w/w
Calcium hydrogen phosphate	19.2%w/w
Lactose	29.0%w/w
Microcrystalline cellulose	5.0%w/w
Povidone K30	6.0%w/w
Colloidal silicon dioxide	0.3%w/w
Magnesium stearate	0.5%w/w

The components, with the exception of the colloidal silicon dioxide and the magnesium stearate, are blended together in a suitable mixer. The powder is then mixed with demineralised water until a granule is formed. The granule is dried and screened to obtain a satisfactory particle size. The screened granule is then blended with the colloidal silicon dioxide and the magnesium stearate.

Bilayer tablets containing 50mg of pethidine hydrochloride weighing 400mg and containing 200mg of Part A and 200mg of Part B, and 10mm in diameter are produced on a tablet press by a two stage compression procedure.

Example 14

Part A

Phenytoin sodium	69.7%w/w
Potato starch	16.5%w/w
Sodium lauryl sulphate	1.0%w/w
Acacia	2.5%w/w
French chalk powdered	9.3%w/w
Magnesium stearate	1.0%w/w

All of the components, except the sodium lauryl sulphate and the magnesium stearate, are mixed together in a blender and then granulated with an 80%v/v solution of ethanol in demineralised water until a satisfactory granule is formed. The granule is dried and passed through a screen to obtain a satisfactory particle size. The screened granule is then blended with the sodium lauryl sulphate and magnesium stearate.

Part B

Phenobarbitone sodium	45.0%w/w
Potato starch	32.0%w/w
Sodium lauryl sulphate	1.0%w/w
Acacia	3.0%w/w
French chalk powdered	18.0%w/w
Magnesium stearate	1.0%w/w

All of the components, except the sodium lauryl sulphate and the magnesium stearate, are mixed together in a blender and then granulated with an 80%v/v solution of ethanol in demineralised water

until a satisfactory granule is formed. The granule is dried and passed through a screen to obtain a satisfactory particle size. The screened granule is then blended with the sodium lauryl sulphate and magnesium stearate.

Part C

Hydroxypropylmethylcellullose	(100,000cp)	40.0%w/w
Calcium hydrogen phosphate		19.2%w/w
Lactose		29.0%w/w
Microcrystalline cellulose		5.0%w/w
Povidone K30		6.0%w/w
Colloidal silicon dioxide		0.3%w/w
Magnesium stearate		0.5%w/w

The components, with the exception of the colloidal silicon dioxide and the magnesium stearate, are blended together in a suitable mixer. The powder is then mixed with demineralised water until a granule is formed. The granule is dried and screened to obtain a satisfactory particle size. The dried granule is then blended with the colloidal silicon dioxide and the magnesium stearate.

Trilayer tablets containing 100mg of phenytoin sodium and 50mg of phenobarbitone sodium, weighing 455mg and containing 144mg of Part A, 111mg of Part B and 200mg of Part C, and 11mm in diameter are produced on a tablet press by a three stage compression procedure.

Comparative Tests

Test 1

Conventional tablets containing 7.5mg zopiclone and weighing 165mg, according to the formula in Table 1, were prepared using a simple wet granulation technique. Bilayer zopiclone tablets containing

hydroxypropylmethylcellulose as a gelling agent (100,000cp) were prepared according to Example 1. The tablet under examination was coarsely crushed using a pestle and mortar and extracted with 2ml of hot or cold water, or an aqueous solution of acetic acid, citric acid or of isopropanol, for 10 minutes. Attempts were made to filter the solutions through a 0.2 micron filter using a syringe. If successful, the concentration of zopiclone in the filtrate was then determined using spectrophotometric measurement at 307nm. The results are summarised in Table 2.

Table 1

Conventional tablet formulation containing 7.5mg zopiclone

Material	Quantity per 100 grams product (g)
Zopiclone	4.55
Lactose	19.45
Calcium hydrogen phosphate	36.36
Maize starch	36.36
Sodium starch glycollate	3.03
Magnesium stearate	0.24

Table 2

Extraction over a 10 minute period of control zopiclone tablets and bilayer zopiclone tablets containing 100,000 cp hydroxypropylmethylcellulose using 2ml of extraction medium.

Extraction Media	Dosage Form	Concent-ration in Filtrate (mg/unit dose)	Percentage zopiclone extracted from tablet
Distilled water	Conventional Tablet	0.40	5.5
	Bilayer Tablet	x	0
Citric acid solution 5%w/v	Conventional Tablet	4.45	56.2
	Bilayer Tablet	x	0
Acetic acid solution 4%w/v	Conventional Tablet	5.02	68.6
	Bilayer Tablet	x	0
isopropanol solution 70%v/v	Conventional Tablet	3.76	32.9
	Bilayer Tablet	x	0

x = not filterable

The results clearly show that, whilst quite substantial levels of zopiclone can be extracted from a conventional tablet, especially when acidic media are used, no filterable solution is present when the bilayer zopiclone tablets of the invention containing a gelling agent are treated with the same medium. The potential for abuse of the tablet product is therefore strictly limited.

Test 2

Dissolution studies were performed on conventional and bilayer zopiclone tablets, as used in Test 1, using the standard USP paddle method operating at a

temperature of 37°C and a rotation speed of 50 r.p.m., with 0.01M hydrochloric acid as the dissolution medium.

Tablets were also prepared according to the formula in Table 3 using standard mixing, granulation and compression techniques to provide a single layer tablet weighing 168mg and containing 7.5mg of zopiclone and the hydroxypropylmethylcellulose gelling agent (10,000 cp)

A comparison of the dissolution results is shown in Table 4.

Table 3

Single Layer Tablet Formulation Containing 7.5mg Zopiclone and a Hydroxypropylmethylcellulose Gelling Agent.

Material	Quantity per 100 grams product (g)
Zopiclone	4.46
Lactose	14.88
Calcium hydrogen phosphate	38.69
Maize starch	17.86
Hydroxypropylmethyl-cellulose (10,000 cp)	14.90
Sodium starch glycollate	8.90
Magnesium stearate	0.30

Table 4

Dissolution data for conventional zopiclone tablets without a gelling agent, bilayer zopiclone tablets containing a hydroxypropylmethylcellulose (100,000 cp) gelling agent and tablets where zopiclone and hydroxypropylmethylcellulose (10,000 cp) are combined in a single layer.

	Approximate Times to Release Stated Percentage of Zopiclone		
Dosage Form	50%	70%	90%
Conventional Zopiclone Tablet	3 mins	5 mins	23 mins
Bilayer Tablet with Gelling Agent	3 mins	4 mins	32 mins
Single Layer Tablet with Gelling Agent	2 hours	No further release up to 12 hours	

The results show that the rate of release of zopiclone from the conventional and bilayer tablets is very similar and that no significant delay is imparted by the presence of the gelling agent. From these results it can be anticipated that the in vivo release and absorption of the two forms would be similar.

The test also demonstrates that the presence of the gelling agent and zopiclone in a single layer results in a serious deterioration of drug release with only 50% of the drug being released after two hours with the remaining drug being trapped in the tablet matrix.

Comparison of the results for the bilayer and the single layer tablets where the zopiclone and gelling agent are mixed together shows that despite the inclusion of a higher viscosity grade of hydroxypropylmethylcellulose (100,000 cp compared to 10,000 cp) release from the bilayer tablet is unaffected.

In summary, it has been demonstrated that the invention provides an abuse resistant tablet which has the dissolution properties of conventional tablets whereas inclusion of the gelling agent in a single layer with the drug substance causes a serious retardation of release.

CLAIMS

1. A tablet containing two or more layers comprising one or more drugs and one or more gelling agents, characterised in that the drug(s) and gelling agent(s) are contained in separate layers of the tablet.

2. A tablet according to Claim 1 in which the gelling agent has a viscosity within the range of about 4,000cp to about 100,000cp.

3. A tablet according to Claim 2 in which the gelling agent has a viscosity within the range of about 10,000cp to about 100,000cp.

4. A tablet according to any previous claim in which the proportion of gelling agent by weight in the gelling layer is from about 20 to about 60%.

5. A tablet according to Claim 4 in which the proportion of gelling agent by weight in the gelling layer is from about 30 to about 50%.

6. A tablet according to any previous claim in which the total amount of gelling layer in the tablet is about 50 to about 80% by weight.

7. A tablet according to any previous claim in which the gelling agent is selected from a modified cellulose, sodium alginate, alginic acid, tragacanth, polyacrylic acid and xanthan, guar, locust bean and karaya gums.

8. A tablet according to Claim 7 in which the gelling agent is selected from hydroxypropylmethylcellulose, carboxymethylcellulose, methylcellulose and xanthane gum.

9. A tablet according to Claim 8 in which the gelling agent is hydroxypropylmethylcellulose.

10. A tablet according to any previous claim in which the drug is selected from analgesics, hypnotics and anxiolytics.

11. A tablet according to Claim 10 in which the drug is selected from zopiclone, temazepam, diazepam, zolpidem, codeine, methadone, pethidine, phenytoin and phenobarbitone.

12. A tablet according to Claim 11 in which the drug is zopiclone.

13, A tablet according to any previous claim having two layers in which one layer comprises a drug and the other layer comprises a gelling agent.

14. A bilayer tablet in which one layer comprises the drug zopiclone and the other layer comprises a gelling agent.

15. A bilayer tablet according to Claim 14 in which the gelling agent is hydroxypropylmethylcellulose.

16. A tablet according to any previous claim also comprising a coating.

17. A tablet according to any previous claim in which the active and gelling layers are substantially identical in colour and appearance.

18. A process for the preparation of a tablet according to Claim 1, which comprises forming the separate active and gelling layers, then combining the

layers in a suitable tabletting machine, optionally followed by the application of a coating using a conventional coating procedure.

19. A method of treating a patient requiring an analgesic, hypnotic or anxiolytic drug, which method comprises administering to said patient said drug comprised within a tablet according to Claim 1.

20. A process for the preparation of a tablet according to Claim 1 substantially as hereinbefore described.

21. A tablet substantially as hereinbefore described with reference to the Examples.

INTERNATIONAL SEARCH REPORT

Interna... al Application No
PCT/GB 95/00137

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE,C,664 908 (SCHÖNTHAN VON PERNWALD) 25 August 1938 see the whole document ---	1,7,8, 13,19
X	EP,A,0 339 420 (BAYER AG) 2 November 1989 see page 4, line 57 - page 6, line 44 ---	1-7,13, 18,20
A	GB,A,2 203 338 (ALZA CORPORATION) 19 October 1988 see the whole document ---	2,3,9,15
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
26 April 1995	12.05.95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Benz, K

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 8316, Derwent Publications Ltd., London, GB; AN 83-38409K & JP,A,58 043 915 (TEIJIN KK) 14 March 1983 see abstract	1,7,8
X	FR,A,2 683 146 (GLAXO GROUP LIMITED) 7 May 1993	1-10,13, 16-21
Y	see page 6, line 14 - page 8, line 4 see page 11, line 22 - page 14, line 30 see page 27; example 2 see page 34 - page 35; example 11	11
Y	DE,A,25 30 563 (BAYER AG) 27 January 1977 see the whole document & US,A,4 070 494 cited in the application	11
Y	US,A,3 980 766 (SHAW ET AL.) 14 September 1976 see the whole document	11

INTERNATIONAL SEARCH REPORT

I ıational application No.
PCT/GB95/00137

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although Claim 19 is directed to a method of treatment of the human /animal body the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/GB 95/00137

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
DE-C-664908		NONE		
EP-A-0339420	02-11-89	DE-A-	3814532	09-11-89
		CA-A-	1333996	17-01-95
		JP-A-	1313427	18-12-89
		US-A-	4966772	30-10-90
GB-A-2203338	19-10-88	US-A-	4786503	22-11-88
		AU-B-	601033	30-08-90
		AU-A-	1406588	06-10-88
		BE-A-	1001699	13-02-90
		CA-A-	1331739	30-08-94
		CH-A-	677447	31-05-91
		DE-A-	3811114	10-11-88
		FR-A-	2613224	07-10-88
		GR-B-	1000053	11-05-90
		JP-A-	63258808	26-10-88
		LU-A-	87189	17-11-88
		NL-A-	8800867	01-11-88
		SE-A-	8801240	07-10-88
		US-A-	4946685	07-08-90
		ZA-A-	8802034	15-09-88
FR-A-2683146	07-05-93	AU-A-	2746992	06-05-93
		BE-A-	1005490	10-08-93
		CA-A-	2081709	01-05-93
		EP-A-	0546593	16-06-93
		GB-A-	2262445	23-06-93
		JP-A-	5194188	03-08-93
		LU-A-	88186	17-05-93
DE-A-2530563	27-01-77	BE-A-	843865	07-01-77
		CA-A-	1064397	16-10-79
		FR-A,B	2361914	17-03-78
		GB-A-	1517480	12-07-78
		JP-A-	52010415	26-01-77
		US-A-	4070494	24-01-78
US-A-4070494	24-01-78	DE-A-	2530563	27-01-77
		BE-A-	843865	07-01-77

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/GB 95/00137

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4070494		CA-A- 1064397	16-10-79
		FR-A,B 2361914	17-03-78
		GB-A- 1517480	12-07-78
		JP-A- 52010415	26-01-77
US-A-3980766	14-09-76	US-A- 3885027	20-05-75